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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/073,596	05/06/1998	RALPH M. STEINMAN	ARG010RC	9977

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/073,596	STEINMAN ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2009 and 11 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99,101,103-113,116,120 and 142-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99,101,103-113,116,120 and 142-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed 12/08/09, and IDS filed 12/11/09, are acknowledged.

2. Claims 99, 101, 104-113, 116, 120, 142-144, and newly added Claim 145, are pending.

3. In view of Applicant's amendment the previous rejection under the second paragraph of 35 U.S.C. 112 has been withdrawn.

4. As set forth previously, The instant application is a continuation in part of U.S. Application Nos. 07/981,357, filed 11/25/1992, and 07/861,612, filed 4/01/92. However, the applications do not disclose the invention of the instant claims. First note that the method step employed in instant Claim 101 comprising, "treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors", is not found in the '612 application. Further, neither the '612 nor the '357 applications disclose the cells being cultured with an antigen as is recited in the last step of Claims 101 and 120. Accordingly, the benefit of priority to said applications is denied. The priority date of the instant application is the filing date of parent application 08/040,677 which is 3/31/1993.

Note that the claims have been amended to recite "modified" antigens and a final "wherein" method step of allowing culture "for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells". This step has not been found in either of the '612 nor '357 applications.

Note that the culturing wherein clause of Claim 101 has been amended to recite an active culturing step.

Applicant's arguments, filed 12/11/09, have been fully considered. Applicant now cites page 22, lines 10-20 of the '612 application in support.

The cite does not provide adequate support for the claimed step. First, it encompasses the production of "antigen activated DCs" and not the production of the mature DCs of Claims 101, 120, and new Claim 45. Mature DCs and antigen-activated DCs are not synonymous. In the instant context it appears that antigen-activation occurs before maturation (which requires additional culture after activation). There is also no disclosure of the modified antigen of the claims. Also note that no support is cited in the '357 application.

Applicant cites original Claims 17 and 36 in the '612 application.

Regarding original Claims 36 and 17 of the '612 application, Claim 17, from which Claim 36 depends, does not recite several of the limitation of instant Claim 101, e.g., mature DCs "derived from an *in vitro* culture of an enriched and expanded population of proliferating DC precursors" nor the "treating the tissue source comprising DC precursors to increase the proportion of DC precursors" nor "culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell aggregates comprising proliferating dendritic cell precursors", etc. Applicant has picked a limitation out of it's original context and attempted to use it here to support the amended claims. Again, no support is cited in the '357 application.

Applicant cites the method disclosed at page 7, line 22 through page 8, line 6 in the '612 application.

A review of the method shows that it does not include the first treating step of Claim 101, nor the final culturing step, nor the wherein clause of the claim. Neither does the cite disclose the modified antigens of the claims.

Applicant cites page 8, lines 15-19 in the '612 application in support of the modified antigens of the claims.

As set forth above, the modified antigens of the instant specification are disclosed only in the context of antigen-activated DCs. And in the instant context it appears that antigen-activation occurs before maturation (which requires additional culture after activation). Thus, antigen-activated DCs are not synonymous with mature DCs.

Accordingly, the benefit of priority is again denied.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 99, 101, 104-113, 116, 120, 142-144, and newly added Claim 145 stand/are rejected under 35 U.S.C. 102(a) as being anticipated by Pancholi et al. (1992).

As set forth previously, Pancholi et al. teaches a pharmaceutical composition comprising human dendritic cells (DCs) pulsed with tuberculosis antigens (see particularly page 218, last paragraph).

The reference clearly anticipates the claimed invention.

Regarding product-by-process claims, MPEP 2113 states:

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and

"The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. *In re Fessmann*, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir.1983).

Applicant's arguments, filed 12/11/09, have been fully considered but are not found persuasive. Applicant argues that the reference is not available as prior art.

Given that the denial of the benefit of priority to the '357 and '612 applications has been maintained, Pancholi et al. (1992) remains available as prior art.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 99, 101, 104-113, 116, 120, 142-144, and newly added Claim 145 stand/are rejected under 35 U.S.C. 103(a) each as

being unpatentable over Inaba et al. (1990, IDS) in view of Steinman et al. (1988, of record) and Markowicz and Engleman (1990, of record).

As set forth previously, Inaba et al. teaches mouse DCs cultured with antigen (see particularly Table 1) that process and express the modified antigen (Table 6, as demonstrated by the cell's ability to prime T cells). The reference further teaches that said pulsed DCs could be useful in "a new approach to immunization" because of their natural adjuvant properties and because the dendritic cell would naturally select the antigen that could be presented on any particular MHC (see page 639, last paragraph).

The reference differs from the claimed invention only in that it does not teach DCs matured in GM-CSF nor human DCs.

Steinman et al. teaches the enrichment and culturing of both mouse and human immature DCs found in blood, as well as bone marrow, (see pages 81-83) and that, "maturation is driven by factors such as IL-1 and GM-CSF" (see page 83). The reference further teaches that "GM-CSF is critical in mobilizing active DCs at the onset of a cell-mediated immune response" (see page 88).

Markowicz and Engleman teach that, "GM-CSF … profoundly affects the morphology and viability of DCs isolated from peripheral blood. GM-CSF not only promotes DC survival but also induces DC differentiation mobile, reversibly adherent cells with long-branched projections. DC cultured in GM-CSF survive for up to 6 weeks and retain their ability to stimulate the proliferation of T cells in allogeneic and autologous MLR" (Abstract). Note that absent GM-CSF these properties were lost (see Figure 5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add GM-CSF to a cell culture of DCs such as the mouse cultures of Inaba et al. and Steinman et al. or the human cultures of Steinman et al. and Markowicz and Engleman. The ordinarily skilled artisan would have added GM-CSF to DC cultures given the teachings of Steinman et al., that, DC "maturation is driven by factors such as IL-1 and GM-CSF", etc. and Markowicz and Engleman, that, "GM-CSF … profoundly affects the morphology and viability of DCs isolated from peripheral blood…". Accordingly, the GM-CSF-cultured DCs as claimed are obvious in view of the combined prior art.

Applicant's arguments, filed 12/11/09, have been fully considered. Applicant argues that Markowicz and Engleman teach away from the claimed invention arguing that the reference suggests that GM-CSF does not cause DCs to divide and proliferate.

Applicant is reminded that the claimed invention is not a method for preparing DCs nor is it a proliferating DC. The claimed invention is a mature DC expressing a modified antigen. Applicant has previously argued that culture in GM-CSF induces properties not seen in other DCs, thus, motivation to culture in GM-CSF, e.g., increased survival, has been provided. Further

note that the motivation of the combined references need not be the motivation of the Inventors.

Applicant argues that Steinman et al. teaches away from the claimed invention arguing that the reference does not teach the method of the instant claims.

Again, the claimed invention is a mature DC expressing a modified antigen. As set forth in the rejection the reference provides motivation for culturing the DCs of Inaba et al. in GM-CSF, thus, resulting in the DCs of the instant claims.

Applicant cites MPEP 2113.

Applicant is advised that the same cite is present in section 6, above.

Applicant argues that the claimed DCs differ from the DCs of Inaba et al. (1990).

Applicant is advised that the rejection is over Inaba et al. (1990) in view of Steinman et al. (1988) and Markowicz and Engleman (1990). Thus motivation to modify the DCs of Inaba et al. has been provided.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 99, 101, 104-113, 116, 120, 142-144, and newly added Claim 145 stand/are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a written description rejection for the introduction of new matter into the claims.

As set forth previously, The specification and the claims as

originally filed do not provide support for the invention as now claimed, specifically, a method step of allowing culture, "for a time sufficient to allow the antigen to bind to the dendritic cells and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells".

Applicant cites page 34, lines 33, through page 35, line 3, of the specification in support.

A review of the cite reveals support for sufficient time to allow binding but not for the additional limitation of sufficient time to process and express the antigen.

Applicant has not addressed this rejection separately.

11. The following new rejection was necessitated by Applicant's amendments.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 120 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, it is unclear whether or not the actions of the claim are actually intended to be method steps. If so, then the steps must be separated and indented as is required of all method steps.

14. No claim is allowed.

15. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0878.

17. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

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